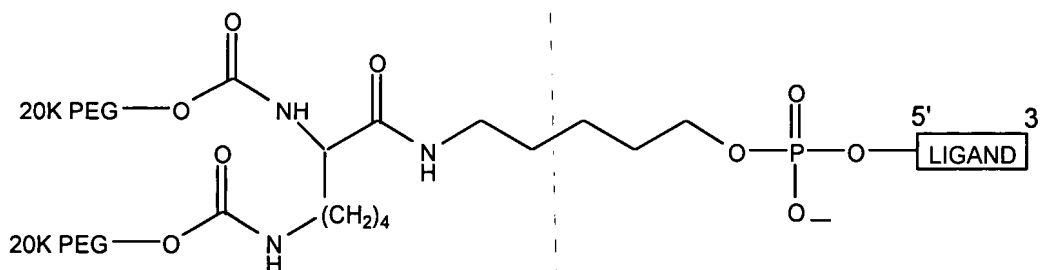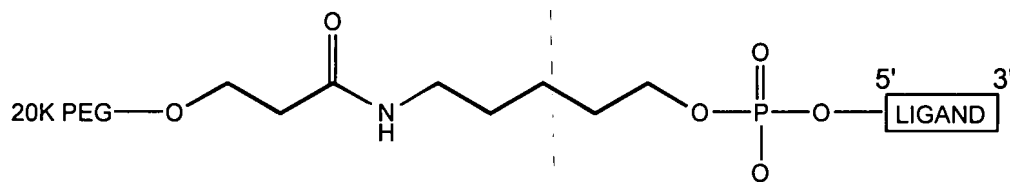20. The method of claim 19 wherein said complex has the structure

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)

21. The complex of claim 19 wherein said complex is

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)

<u>REMARKS</u>

An Office Action was issued in the above-referenced application on June 8, 1998. All examined claims were rejected. This Amendment and Remarks has been made to respond to such Office Action. Claim 2 is amended and claims 3-21 are added herein. Additional amendments have been made by the Applicants without suggestion by the Examiner, but with the same goal in mind. Any amendments that are made that limit the scope of the claims in any way are done so without prejudice. Claims 3-21 are dependent on either claim 1 or claim 2 and relate to embodiments that are clearly supported in the specification.

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Notice to Comply with Sequence Rules

Applicants submitted a response to the Notice to Comply with Requirements for Patent Applications containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures on July 7, 1998.

Informalities

The Examiner has objected to the disclosure because nucleotide sequences in the specification, tables and figures lack SEQ ID NOS. Applicants have added the appropriate SEQ ID NOS to Tables 1-4 and Figures 1A-1E and are submitting substitute tables and figures with this document. Furthermore, the specification has been amended to include SEQ ID NOS where appropriate. Applicants assert that the amendments and the substitute tables and figures do not add any new matter to the application or affect the claimed invention. Withdrawal of this objection is respectfully requested.

Rejections under 35 U.S.C. §112, second paragraph

Claim 2 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim has been amended to specifically address points (a), (b), and (d).

With respect to point (c), the Examiner states that the claim is indefinite in reciting "nucleic acid ligand" which is a general term lacking definition or specificity. Applicants respectfully disagree. Applicants wish to direct the Examiner's attention to page 17, lines 4-26 of the specification where Nucleic Acid Ligand is specifically defined. There is no apparent ambiguity with respect to the definition of this term. As this term has been clearly defined in the specification, withdrawal of this rejection is respectfully requested.

Double Patenting Rejection - Obviousness Type

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 and 11-13 of United States Patent Application No. 08/447,169 (now United States Patent No. 5,811,533) in view of Toole et al. (WO 92/14843). In an effort to expedite prosecution,
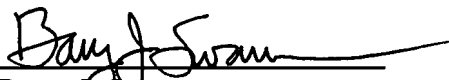
Applicants are submitting herewith a Terminal Disclaimer that disclaims the term of the patent issuing on the subject application beyond the term of the aforementioned patent. NeXstar Pharmaceuticals, Inc., is the assignee of record of the entire interest in United States Patent No. 5,811,533. Thus, NeXstar Pharmaceuticals, Inc. is the owner of the subject application and the patent cited by the Examiner. In view of this submission, it is respectfully requested that the provisional obviousness-type double patenting rejection be withdrawn.

Applicants assert that the above-captioned application is in condition for allowance. Prompt consideration of this Amendment and Remarks is earnestly solicited.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to Deposit Account No. 22-0277, if not otherwise specifically requested. In addition, the undersigned hereby authorizes the charge of any fee created by the filing of this document to Deposit Account No. 22-0277.

Respectfully submitted,

Date: December 7, 1998

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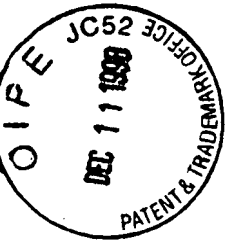nexstar\nex61cip\amendment.351/tec wrd

8

Table 1. 2'-F-pyrimidine ligands to VEGF165

Ligand (frequency)	Sequence of variable region 5'-gggaggacgaugcgg [variable region] cagacgacugcccga-3'			Kd (pM)	SEQ. ID NO: 10 & 11
Family 1					
VP30.7	g	gAAGAAUUGG	UCAUCGUCGUCUCCGCCUCCC	3000	12
VP30.12	AAUACG	GAAGAAUUGG	AUACAUAUGCUCGU	7	13
VP30.13 (7)	GAUAACA	GAAGAAUUGG	UGAACAACGUGGU	10	14
VP30.16	AUGAUCGCGUAG	GAAGUAUUGG	AAGGCCCU	6	15
VP30.19	CACUUA	GAAGAAUUGA	AUUUCCCGCUGGU	9	16
VP30.22 (6)	UAG	GAAGAAUUGG	AAGGGGAUUUCCUCGU	20	17
VP30.25	CGGGAUUUG	GAAGAAUUGG	AUAUGGCCU	20	18
VP30.26 (2)	CGGYACUUUG	GAAGAAUUGA	AUUUCCCGCU	10	19
VP30.27	g	gAAGAAUUGG	AUAUAUCGUUCACCCCACCU	400	20
VP30.40	AAACG	GAAGAAUUGG	AUACGCAAGCACGU	6	21
VP30.41	UAG	GAAGUAUUGU	AAGGCGCCUCGUUUUGC	7	22
VP30.51 (2)	AGUUUUG	GAAGAAUUGG	AUGUUCGAUCGU	90	23
VP30.54	AAGAAACG	GAAGAAUUGG	AGACACGCUCGU	10	24
VP40.4 (5)	g	GAAGAAUUGA	UGUUGUAUUGUCCUUCGAUUUCCUGCCGU	200	25
VP40.43	ACA	GAAGAAUUGG	GCUUCGCAUUAUCCUCUGUCAGCCGC	30	26
VP40.53	UGAGAGAAACG	GAAGAAUUGG	AUACGAUACUCAUCGCGCU	8	27
VT30.4	CUUAAGUUUUG	GAAGAAUUGA	AUACUGGGU	20	28
VT30.7	UAACCAGUG	GAAGAAUUGG	CUGCUAUCCU	10	29
VT30.10	AACG	GAAGAAUUGG	AUACGUAGCAUGCGU	2	30
VT30.13	CAGGAUUUUG	GAAGAAUUGG	AUAUUGGCCGca	10	31
VT30.20	AAACG	GAAGAAUUGG	AUACCGCUACGUGUU	4	32
VT30.52	g	gAAGAAUUGA	GCAUUCCUUCUCCUUGUGCCU	9000	33
VT30.53	AGCUAACG	GAAGAAUUGG	AAACAACCGCGUc	10	34

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APPROVED SZ 8-29-99

Ligand (frequency)	Sequence of variable region 5'-gggaggacgaugcgg [variable region] cagagcacucgcccga-3'	Kd (pM)	SEQ. ID. NO: 10 & 11
Family 2			
VP30.2 (5)	ggYGA ACCGA UGGAA UUU UUGGACGC UGGGACGC UCGCCU	10	35
VP30.5 (4)	gAYCA ACCGA UUGAC GUUA UGGGACGC UGGUc	8	36
VP30.31 (5)	gcggUA ACCGA UUGAA CUUC UUGGACGC UACCGU	6	37
VP30.43	ggUA ACCGAA UUGAA GUUA UUGGACGC UACCU	5	38
VP40.9	gGAGCAGA ACCGA UAGAA GAA UUGGACGC UCAGCUCGGGU	30	39
VP40.14	GUACCAGAAUGAGCA ACCGA AUGAA GAA CUGGACGC UGCUca	8	40
VP40.17	ugcggUGA ACCGA UGGAA UCGC UUGGACGC UCAUCGCACGUUGCU	10	41
VT30.9 (6)	ggUCA ACCGG UUGAA UAU UUGGUCGC UGACCU	30	42
Family 3			
VT30.1 (2)	gacgaugcgg A ACUA GUGAAUGCUU AUA CGA CCGUGUUGUc	10	43
VT30.2	gcgg AUCA GUGAAUGCUU AUA GA CCGCCUCCGU	2	44
VT30.3 (8)	gaugcgg AGA AUCA GUGAAUGCUU AUA AAUC UCGYGUc	5	45
VT30.11	gaugcgg A AUCA GUGAAUGCUU AUA GCUC CCGGUCCU	4	46
VT30.15	gcgg A ACCA GUGAAUGCUU AUA AGA CUGCUCGU	3	47
VT30.21	cgaugcgg AUCA GUGAAUGCUU AUA GA CCGUAUUGCGU	6	48
VT30.28	gaugcgg AGA AUCA GUGAAUGCUU AUA AACC UCGUGUc	60	49
VT30.29	augcggA AUCA GUGAAUGCUU AUA GC UCCGCGUGGU	10	50
VT30.35	cgg ACCA GUGAAUGCUU AUA AGCCCA UCGACCU	N.D.	51
VT30.41	gaugcgg CAGG GUGAAUGCCA AUG UACUUU UCGCGUc	40	52
VT30.44	gcggA AUCA GUGAAUGCUU AUA* CA UCCGUCGGU	10	53
VT30.54	gcggG ACUAG GUGAAUGCCA AUA UUCUUC UCCGU	10	54

Table 2. Effect of truncation on high affinity binding of VEGF ligands.

Ligand	Sequence	Length (nts)	KD (pM)	SEQ ID NO:
t22	GACGAUGCGGUAGGAAGAAUUGGAAGCGC*	29	70	55
t22a	GACGAUGCGGUAGGAAGAAUUGGAAGCG	28	3000	56
t22b	ACGAUGCGGUAGGAAGAAUUGGAAGCG<u>C</u>	28	80	57
t22c	GCGGUAGGAAGAAUUGGAAGCG<u>C</u>	23	90	58
t22d	CGGUAGGAAGAAUUGGAAGCG<u>C</u>	22	100	59
t22e	GGUAGGAAGAAUUGGAAGCGC*	21	200	60
t22f	GUAGGAAGAAUUGGAAGCGC*	20	>100,000	61
t2	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC*	31	20	62
t2a	GCGAACCGAUGGAAUUUUUGGACGCUCG<u>C</u>	29	40	63
t2b	CGAACCGAUGGAAUUUUUGGACGCUCG	27	100	64
t2c	GAACCGAUGGAAUUUUUGGACGCUC*	25	200	65
t2d	AACCGAUGGAAUUUUUGGACGCU*	23	20,000	66
t2e	ACCGAUGGAAUUUUUGGACGC*	21	>100,000	67
t44	GCGGAAUCAGUGAAUGCUUAUACAUCCGC*	29	10	68
t44a	CGGAAUCAGUGAAUGCUUAUACAUCCG	27	10	69
t44b	GGAAUCAGUGAAUGCUUAUACAUC<u>C</u>	25	60	70
t44c	GAAUCAGUGAAUGCUUAUACAUC*	23	2000	71
t44d	AAUCAGUGAAUGCUUAUACAU*	21	>100,000	72
t44e	AUCAGUGAAUGCUUAUACA*	19	>100,000	73

Table 3. Effect of 2'-OMe-purine substitutions on affinity for VEGF.

Ligand	Sequence	K_D (pM)	SEQ NO:
t22OMe (OH-10,12,22)	GACGAUGCGGUAGGAAGAAUUGGAAGCGC	10	74
t22OMe (OH-10,12)	GACGAUGCGGUAGGAAGAAUUGGAAGCGC	20	75
t22OMe (OH-10,22)	GACGAUGCGGUAGGAAGAAUUGGAAGCGC	4,000	76
t22OMe (OH-12,22)	GACGAUGCGGUAGGAAGAAUUGGAAGCGC	90	77
t2OMe (OH-6,21)	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC	60	78
t2OMe (OH-6)	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC	500	79
t2OMe (OH-21)	GGCGAACCGAUGGAAUUUUUGGACGCUCGCC	20,000	80
t44OMe (OH-5,6)	GCGGAAUCAGUGAAUGCUUAUACAUCCGC	40	81
t44OMe (OH-5)	GCGGAAUCAGUGAAUGCUUAUACAUCCGC	>100,000	82
t44OMe (OH-6)	GCGGAAUCAGUGAAUGCUUAUACAUCCGC	>100,000	83

**Table 4. Binding Parameters of 2'-Ome-substituted minimal ligands.**

| Ligand	Sequence	K_D (s.d.) (pM)	k_d (s.d.) (sec^{-1})	k_a (M^{-1}sec^{-1})	SEQ ID NO:
t22OMe	GCGGUAGGAAGAAUUGGAAGCGC	67 (36)	0.012 (0.004)	1.8×10^8	84
t2OMe	GCGAACCGAUGGAAUUUUGGACGCUCGC	140 (50)	0.0042 (0.002)	3.0×10^7	85
t44OMe	CGGAAUCAGUGAAUGCUUAUACAUCCG	51 (11)	0.0074 (0.002)	1.5×10^8	86
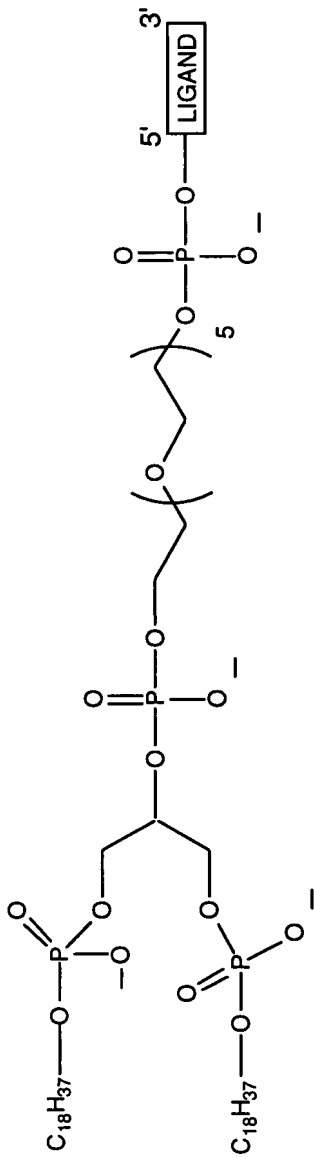
67

NX31838 - PL

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAfUmGfCfUfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)

FIGURE 1A   SEQ. ID NO.: 5
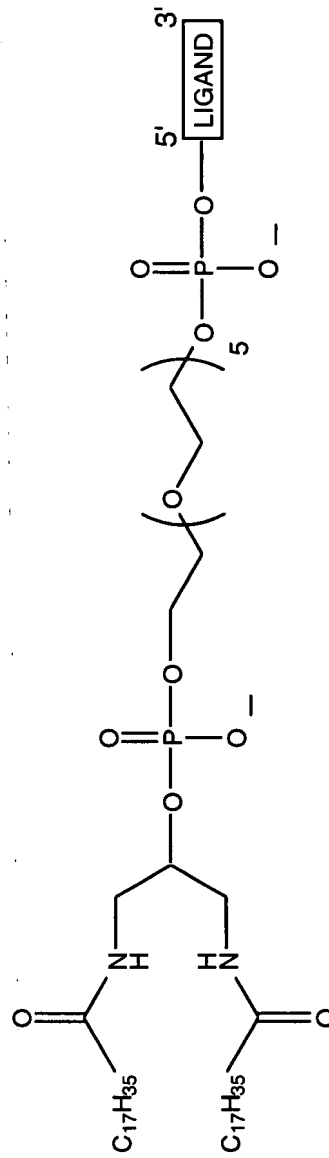
5' LIGAND 3'

NX31838 Lipid-amide 1

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAfUmGfCfUfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)
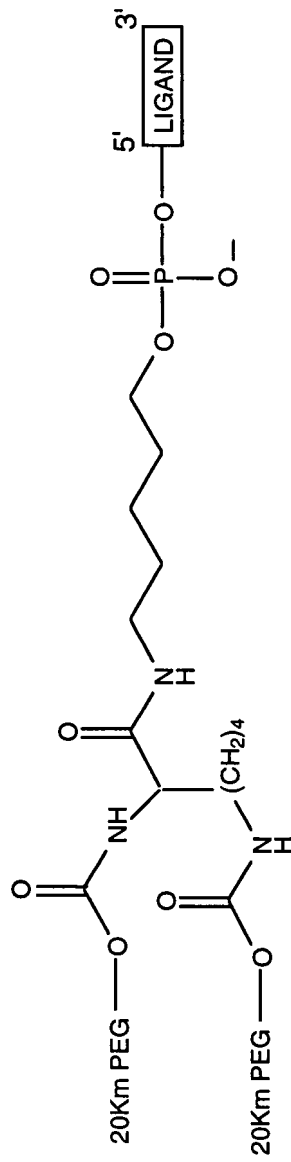
FIGURE 1B   SEQ. ID NO.:6
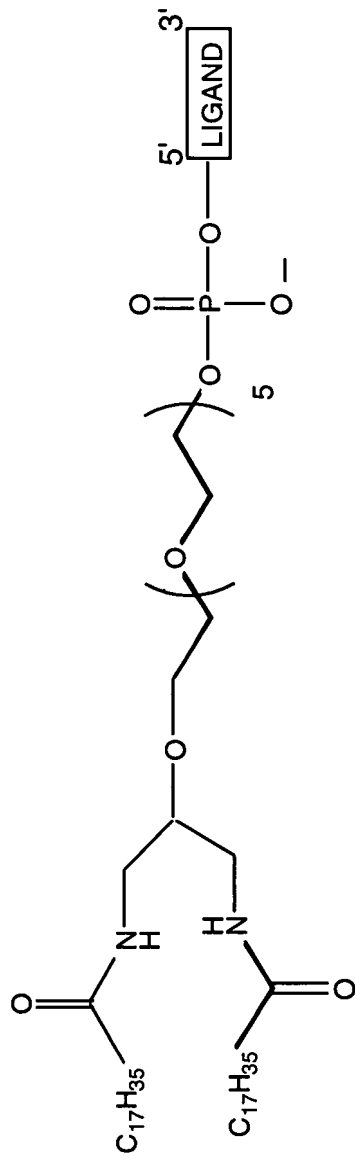
5' LIGAND 3'

NX31838 Lipid-amide 2

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)

FIGURE 1C   SEQ. ID NO.: 7

NX31838   40K mPEG

Ligand Component =
fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfCmAfUfCfCmG-3'3'-dT
(VEGF ligand)

FIGURE 1D   SEQ. ID NO.: 8

20Km PEG—O

5' 3'

LIGAND

NX31838   20Km PEG
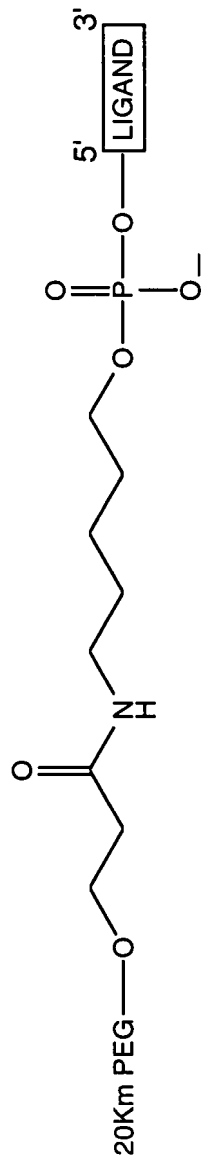
Ligand Component =

fCmGmGrArAfUfCmAmGfUmGmAmAfUmGfCfUfUmAfUmAfCmAfUfCfCmG-3'3'-dT

(VEGF ligand)

FIGURE 1E   SEQ. ID NO.: 9